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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/393,302	09/10/1999	ARA HOVANESSIAN	03495.0166-0	2522

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EXAMINER
ZEMAN, ROBERT

ART UNIT	PAPER NUMBER
1645	20

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/393,302	Applicant(s) HOVANESSIAN ET AL.	
	Examiner Robert A Zeman	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1,7,8,11-12 and 14-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2-6,9,10 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1-23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed on 2-28-2002 is acknowledged. Claims 2, 4-6, 9-10, 13 and 23 have been amended. Claims 1-23 are pending. Claims 1, 7-8, 11-12 and 14-23 have been withdrawn from consideration. Claims 2-6, 9-10 and 13 are currently under examination.

Objections Withdrawn

The objection to the disclosure for improperly labeling the Brief Description of Drawings section is withdrawn in light of the amendment thereto.

The objection to claims 5-6, 9-10 and 13 for misuse of the term "anyone" is withdrawn in light of the amendment thereto.

The objection to claims 2 for being dependent on non-elected inventions is withdrawn in light of the amendment thereto.

The objection to claims 4 and 9 under 37 CFR 1.75(c) as being in improper form for failing to refer to other claims in the alternative only is withdrawn in light of the amendment thereto.

The objection to claims 6, 9, 10 and 13 under 37 CFR 1.75(c) as being in improper form for reciting having a multiple dependent claim depend from another multiple dependent claim is withdrawn in light of the amendment thereto.

Objections Maintained

The objection to the specification for failing to comply with 37 C.F.R. 1.821(d) is maintained for reasons of record. As of May 3, 2001, corrections to drawings cannot be held in abeyance

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

The objection to claims 3-6, 9-10 and 13 for being dependent on non-elected inventions is maintained for reasons of record. Specifically, claim 3 and 9 are dependent on non-elected inventions (P40/PHAII and P30/PHAPI).

Claim Rejections Withdrawn

The rejection of claim 2 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrases "**modify the interaction** between, **on the one hand** the V3 loop receptor according to claim 1 present on **the cell surface of a patient** infected with a **human HIV retrovirus,** specifically HIV-1 or HIV-2, and **on the other hand** the gp120 envelope protein of said HIV retrovirus" is withdrawn in light of the amendment thereto.

The rejection of claim 4 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "which consists in a peptide or pseudopeptide" is withdrawn in light of the amendment thereto.

Claim 4 is rendered vague and indefinite by the use of the phrase " amino acid additions, deletions and or substitutions in the amino acid sequence of the inhibitor molecules according to claim 3". It is unclear what Applicant is referring to since claim 3 does not describe alterations of an amino acid sequence.

The rejection of claim 5 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "peptide bond is modified and replaced" is withdrawn in light of the amendment thereto.

The rejection of claim 5 under 35 U.S.C. 112, second paragraph, for reciting improper Markush language is withdrawn in light of the amendment thereto.

The rejection of Claim 6 under 35 U.S.C. 112, second paragraph, as being is rendered vague and indefinite by the use of the phrase "chosen among" is withdrawn in light of the amendment thereto.

The rejection of claims 6 and 9 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "derived from" is withdrawn in light of the amendment thereto.

The rejection of claim 9 under 35 U.S.C. 112, second paragraph, as being vague and indefinite by the use of the phrase "sequence of interest" is withdrawn in light of the amendment thereto.

The rejection of claim 9 under 35 U.S.C. 112, second paragraph, as being vague and indefinite by the use of the phrases "preferably 4 to 15 monomer units " and "more preferably 5 to 10 monomer units" is withdrawn in light of the amendment thereto.

The rejection of claim 10 under 35 U.S.C. 112, second paragraph, as being vague and indefinite by the use of the phrase "under the form" is withdrawn in light of the amendment thereto.

The rejection of claim 13 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "such as" is withdrawn in light of the amendment thereto.

Claim Rejections Maintained and New Grounds of Rejection

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The aforementioned claim is drawn to therapeutic compositions comprising inhibitor molecules and encompasses pharmaceutical use in humans for prevention and/or treatment of HIV infection. People of skill in the art require documented factual evidence, that a benefit can be derived by the therapeutic application of a substance. The instant specification discloses a multitude of *in vitro* studies to illustrate the mode of action of claimed peptides/pseudopeptides. The specification discloses studies to demonstrate that said peptides/pseudopeptides inhibit HIV membrane fusion by binding to a cell-surface protein. (p95). The specification further discloses various studies that characterize the chemical/biological properties of p95, its role in HIV pathogenesis and its interaction with the instant peptides/pseudopeptides. The specification is silent on the efficacy of the instant invention when used *in* vivo. The instant specification fails to provide direction on what peptides or polypeptides, if any, are capable of eliciting a therapeutic immune response or that a given response would be beneficial to the treated subject. Moreover, the specification is equally silent on how said peptides or polypeptides are to be administered. Applicant has failed give direction on what peptides, if any, would meet the limitations of the claims or how to administer any suitable peptides in order to elicit the desired immune response and has provided no evidence that any benefit to the treated subject would be obtained. Additionally, the specification fails to provide a basis, if one exists, for correlating the *in vitro* data with, or extrapolating to, human HIV treatment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-6, 9-10 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claim 2 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "peptidic or non-peptidic inhibitor molecule" is maintained for reasons of record.

Applicant argues:

1. Peptide is defined as "any of various natural or synthetic compounds containing 2 or more amino acids linked by the carboxyl group of one amino acid and the amino group of another".

2. Said terms describe the inhibitor molecule and clarify that the inhibitor can be a peptide or a non-peptide.

Applicant's argument has been fully considered and deemed non-persuasive. It is unclear to what Applicant is referring. Is applicant claiming all compounds/chemicals that may "modify the interaction between the HIV receptor and the gp120 envelope glycoprotein"? As written, it is impossible to determine the metes and bounds of the claimed invention.

The rejection claim 3 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "peptide fragment" is maintained for reasons of record. Contrary to Applicant's assertion, said claim has not been amended. Consequently it is still unclear what is meant by said term.

The rejection of claim 3 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "pseudopeptide counterpart" is maintained for reasons of record. Applicant has based his arguments on a reference not of record. Contrary to Applicant's assertion, the reference Callebaut et al., Virology 218:181-192, 1996 was not enclosed with the instant amendment. However, while said reference describes what constitutes a pseudopeptide, said reference does not disclose what constitutes a "pseudopeptide counterpart". Applicant argues that "counterpart" refers to "the fact that peptide fragment **could** have structural and/or functional homology". Since said homology is not a limitation of the rejected claim, Applicant's argument is not on point.

The rejection of claim 3 for reciting improper Markush language is maintained for reasons of record. Applicant did not address the aforementioned rejection in his response.

The rejection of claim 4 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "pseudopeptide which is homologous" is maintained for reasons of record.

Applicant argues:

1. Said pseudopeptide has sequence homology to the inhibitor of claim 3 but is not identical in that it has at least one amino acid sequence addition, deletion or substitution.

Applicant's arguments have been fully considered and deemed non-persuasive. Contrary to Applicant's assertion said claim does not recite the limitation of "sequence homology". Additionally, it is unclear how many amino acid sequence "differences" can be incorporated before a "homologous" pseudopeptide become unrelated.

The rejection of claim 6 under 35 U.S.C. 112, second paragraph, for reciting improper Markush language is maintained for reasons of record. The amendment to said claim is insufficient to overcome the aforementioned rejection. The listing of group members should be preceded by "**selected from**" or "selected from the group consisting of" and the final member of the Markush group should be preceded by an "**or**" or an "and", respectively.

Claim 2 is rendered vague and indefinite by the use of the term "inhibitor is not nuclear nucleolin. One cannot define a limitation of an invention by what it "is not" as long as it remains unclear what the invention **is.** Consequently, it is impossible to determine the metes and bounds of the claimed invention.

Claim 2 is rendered vague and indefinite by the use of the term "able to". Having the ability to do something is not equivalent to actually doing it. Consequently, it is impossible to determine the metes and bounds of the claimed invention.

Claim 6 is rendered vague and indefinite by its recitation of various amino acid positions of SEQ ID NO:1. SEQ ID NO:1 recites a nucleic acid sequence not an amino acid sequence. Additionally, said sequence is only 30 nucleotides long and therefore cannot have position number 44, 171, 209 or 271.

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant invention is drawn to various fragments of nucleolin that function to inhibit interaction between gp120 of the HIV retroviruses and the V3 loop (nucleolin).

The rejection of claims 2-4, 6, 10 and 13 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Suzuki et al. (Biochemical Journal, Vol. 289 Part 1, pages 109-115, January 1, 1993) is maintained for reasons of record.

Applicant argues:

1. The amended claims read on cytoplasmic nucleolin not nuclear nucleolin described in the cited reference.

2. Cytoplasmic and nuclear nucleolin are distinguishable by their respective pI values.

3. The 60 kD fraction disclosed by Suzuki et al. originates in the N-terminal region of the nucleolin molecule whereas the 60kd portion of cytoplasmic nucleolin originates in the C-terminal region.

Applicant's arguments have been fully considered and deemed non-persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., inhibitor is cytoplasmic nucleolin) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Suzuki et al. disclose a method whereby they generated fragments of nucleolin. Said method included: cleavage of purified nucleolin by *N*-bromosuccinimde (NBS) or endogenous proteases; separation of fragments on SDS/PAGE; digestion of the resulting fragments (bands) with V8 protease (see pages 109-110). Since the entire nucleolin protein was digested, in absence of evidence to the contrary, the method of Suzuki et al. would generate all of the peptides/fragments of the claimed invention. While Suzuki et al. do not specifically describe using their peptide/fragments for the inhibition of gp120/nucleolin binding, it would be an inherent property of the fragment. Determination of the biological/chemical properties of each peptide/fragment would be obvious to one of skill in the art.

The rejection of claims 2-4, 6, 9-10 and 13 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sapp et al. (European Journal of Biochemistry, Vol. 179 No. 3, pages 541-548, February 15, 1989) is maintained for reasons of record.

Applicant argues:

1. The amended claims read on cytoplasmic nucleolin not nuclear nucleolin described in the cited reference.

2. There is no indication that the nucleolin described by Sapp et al. would posses the claimed HIV inhibitory activities.

3. Sapp does not disclose the existence of nucleolin that functions extracellularly.

Applicant's argument has been fully considered and deemed non-persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., inhibitor is cytoplasmic nucleolin that functions extracellularly) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Sapp et al. disclose a method whereby they generated fragments of nucleolin. Said method included the cleavage of purified nucleolin endogenous proteases and the sequencing of the resulting fragments (see page 542). Since the entire nucleolin protein was digested, in absence of evidence to the contrary, the method of Sapp et al. would generate all of the peptides/fragments of the claimed invention. While Sapp et al. do not specifically describe using

their peptide/fragments for the inhibition of gp120/nucleolin binding, it would be an inherent property of the fragment. Determination of the biological/chemical properties of each peptide/fragment would be obvious to one of skill in the art.

Claims 2-4, 6, 9-10 and 13 rejected under 35 U.S.C. 102(a) as being anticipated by Callebaut et al. (Virology Vol. 218, No. 1 pages 181-192, 1996).

Callebaut et al. disclose the use of pseudopeptides for inhibiting the HIV entry (infection) by interfering with the binding between gp120 and the cellular receptor.

35 USC § 103

The rejection of claims 2-6, 9-10 and 13 under 35 U.S.C. 103(a) as being unpatentable over Srivastava et al. (FEBS Letters, Vol. 250 No.1, pages 99-105, 1989) is maintained for reasons of record.

Applicant argues:

1. The amended claims read on cytoplasmic nucleolin not nuclear nucleolin described in the cited reference.

Applicant's argument has been fully considered and deemed non-persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., inhibitor is cytoplasmic nucleolin) are not recited in the rejected claim(s). Although the claims are

interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Srivastava et al. disclose the complete nucleotide and amino acid sequence for human nucleolin (see page 101). Srivastava et al. further disclose a comparison between nucleolin from humans, chickens and hamsters. Since the entire nucleolin protein was incorporated in the cDNA library (see page 109), in absence of evidence to the contrary, said library would generate all of the peptides/fragments of the claimed invention. While Srivastava et al. do not specifically describe using their peptide/fragments for the inhibition of gp120/nucleolin binding, it would be an inherent property of the fragment. Determination of the biological/chemical properties of each peptide/fragment would be obvious to one of skill in the art. Additionally, since Srivastava et al. knew the sequences of the cDNA fragments (see page 109), it would have been obvious to one of skill in the art to modify said sequence so that the resulting peptide would have enhanced stability etc. One would have been motivated to make such modifications in order to protect said peptides from endogenous proteases thus increasing the half-life of said peptides.

Claims 2-4, 6, 9-10 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rankin et al. (Nucleic Acids Research, Vol. 21 No. 1, page 169).

Rankin et al. disclose the full-length cDNA sequence of nucleolin. Rankin et al. differ from the instant invention in that they don't disclose the specific peptides. However, it would have been obvious for one of skill in the art to use the disclosed sequence to produce

polypeptides. Said reference reads on all the rejected claims since said claims recite open claim language.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on M-Th 7:30 am - 5:00 pm and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donna Wortman can be reached on (703) 308-1032. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman
May 6, 2002